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EXAMINER	
BARTON, JEFFREY THOMAS	
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1753	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	**Application No.** 10/057,354	**Applicant(s)** BOHM ET AL.	
	Examiner Jeffrey T. Barton	**Art Unit** 1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-24,26-48 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-24,26-48 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 December 2006 has been entered.

Response to Amendment

2. The response filed on 11 December 2006 does not place the application in condition for allowance.

Status of Rejections Pending Since the Office Action of 11 July 2006

3. The rejections of claims 30-37 under 35 U.S.C. §103(a) as unpatentable over Heller et al in view of either McCormick et al or Amigo is withdrawn upon review of the claim language and respective disclosures.

4. All rejections based on Simpson et al in view of Heller et al are withdrawn upon review of the respective disclosures.

5. All other previous rejections are maintained.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 50 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is no disclosure of the meniscus described in this claim in the application as originally filed. The figures uniformly show menisci with outer edges aligned with the bottom of the injection port, with the lowest point of the meniscus aligned with no portion of the sidewall. The specification text provides only the most general description of meniscus shape (Page 10, lines 6-20), with no explicit description of "an inner edge of the meniscus align[ed] with an inner surface of the side wall and an outer edge of the meniscus align[ed] with an outer edge of the side wall". Contrary to Applicant's arguments, description of a meniscus essentially replacing the removed portion of the sidewall provides no support for the detailed meniscus positioning recited in this claim. Other meniscus positions (i.e. those shown in the instant figures) can be equally well described as replacing the removed portion of the sidewall.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-3, 5-24, and 26-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (US Patent No. 6,627,406)

In this rejection, undue weight cannot be given to the recitation of “separation” channels. Specifying an intended use, such as separation, does not structurally define the channels. Therefore, channels having ports as claimed are considered to read on the claims, since they are structurally capable of performing separation.

Singh et al teach a separation device comprising one or more reservoirs (Figures 6A-6C; reservoirs 602, 604, or 606) and a plurality of channels connected to the reservoirs (608, 610) having an interior bounded by a side wall (Plate 614); fluid interface ports (612) formed in the side wall of a channel, each port having a depth equal to a thickness of the side wall, and a diameter significantly larger than the depth (Example using system of Figure 6; Column 34, line 65 - Column 35, line 17); wherein a medium disposed in the channel forms a virtual wall at the fluid interface port having a meniscus that is substantially co-planar with the side wall of the channel and each fluid interface port has a dead volume of less than about 1 picoliter. (Column 29, lines 6-14; dead volume is inherent with fluid not traveling into the port, no structural difference exists between the claims and the structure of Singh et al) Singh et al teach several channel systems with reservoirs multiplexed to numerous channels. (e.g. Figures 3 and 9-11) Regarding claims 14, 15, and 21, the devices of Singh et al are disclosed as being made from a glass or plastic plate having channels formed therein and a cover plate of the same or different material. (Column 12, lines 36-43)

Regarding claim 39, Singh et al teach providing a device which will form a meniscus "virtual wall" as required in the claims, as described above.

Singh et al do not explicitly disclose the reservoirs of Figure 6 being anode or cathode reservoirs, nor do they explicitly teach channels multiplexed to reservoirs in the system of Figure 6. Regarding claim 12, Singh et al do not explicitly disclose the arrays of reservoirs in the system of Figure 6. Regarding claim 39, Singh et al do not explicitly disclose the forming and directing steps within the description of Figure 6.

Singh et al teach the optional provision of electrodes to the reservoirs of their systems for providing electrokinetic fluid motion. (Column 21, lines 8-25 and Column 22, lines 32-50) Singh et al also teach multiplexing the channels of their systems (e.g. Figures 3 and 9-11; Column 6, lines 17-38) to provide flexibility in operation, such as delivery of agents to zones for reaction. Regarding claim 12, Singh et al also teach providing a plurality of channel systems in an array on a substrate. (Figures 11-14) Regarding claim 39, Singh et al disclose forming droplets and directing these droplets of liquid to a zone to make immediate contact with fluid in the channels. (Column 7, line 66 - Column 8, line 5)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the system of Figure 6 of Singh et al by providing electrodes to the reservoirs, as suggested by Singh et al, because it would provide the ability to manipulate the fluids in the device electrokinetically, as suggested by Singh et al (Column 21, lines 8-25 and Column 22, lines 32-50)

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to modify the system of Figure 6 of Singh et al by multiplexing the channels to numerous other channels and reservoirs, as suggested by Singh et al, because Singh et al teach that this provides desirable flexibility in operation, such as in delivery of different materials to zones for reaction. (Figures 3 and 9-11; Column 6, lines 17-38)

Such provision of electrodes and multiplexing of the channel systems meets the limitations to independent claims 1, 30, 32, 40, 43, and 46-48.

Specific to claim 12, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Figure 6 of Singh et al by providing an array of devices on a single substrate, as shown by Singh et al in Figures 11-14, because such a device geometry would allow facile parallel analyses, the advantageousness of which would have been apparent to anyone having ordinary skill in the art of biochemical analysis.

Specific to claim 39, in the obvious multiplexed system, it would have been obvious to add the required solutions (Column 29, lines 9-11) as droplets directed to the liquid in the channel, as suggested by Singh et al (Column 7, line 66 - Column 8, line 5), because Singh et al suggest this means of adding solutions to the systems of their invention.

Regarding claims 2, 16, 22, 24, and 34, Singh et al suggest such an array. (Column 22, lines 33-40)

Regarding claim 3, the multiplexed systems connect outer regions to inner regions. (Figures 3 and 9-11)

Regarding claim 5, with no fluid travel into ports 612, the dead volume will be zero. (Column 29, lines 7-9)

Regarding claims 6 and 23, Figures 6a and 6c show such an array of ports.

Regarding claims 7, 13, 31, 33, 41, and 44, such choice of size with no change in device operation does not result in patentable distinction over the prior art. In *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 830, 225 USPQ 232 (1984), the Federal Circuit held that, where the only difference between the prior art and the claims was a recitation of relative dimensions of the claimed device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device was not patentably distinct from the prior art device.

Regarding claims 8-11 and 26-29, Singh et al disclose the systems performing such a variety of analyses. (Column 22, lines 51-55; Column 21, lines 13-25) Regardless, the recitation of an intended use of the device does not further structurally define the device, and the claims are rendered obvious for the reasons given for claims 1 and 12.

Regarding claims 17 and 19, Singh et al also suggest an electrode array integral to the two substrates. (Column 22, lines 33-40; "painting" electrodes) Such an array would have a particular alignment relative to the reservoirs and ports as claimed in claim 19.

Regarding claims 18 and 35-37, Figures 6a and 6c show regular spacing of the ports. The limitation to a loading device, such as a pipetter or pin, corresponds to intended use, and cannot be given significant weight. The arrangement shown in the figures is considered to be "configured" or "adapted" appropriately for such use.

Regarding claim 20, Figure 6 shows only holes that are reservoirs, which could obviously have electrodes (i.e. anodes or cathodes) as discussed above, or ports. Singh et al disclose adding samples to each port. (Column 29, lines 9-11) Therefore, the number of holes is as claimed.

Regarding claims 38, 42, and 45, choice of a radial or other conventional channel pattern is a matter of design choice to a skilled artisan based on which design is most suitable for the peripheral devices to be used with the system. In the absence of evidence that the shape is significant to system operation, such selection of shape does not confer patentability. For instance, in *In re Dailey*, 357 F.2d 669, 149 USPQ 47 (CCPA 1966), the court held that the configuration of the claimed object was a matter of choice which a person of ordinary skill in the art would have found obvious absent persuasive evidence that the particular configuration of the claimed container was significant.

12. Claims 1-3, 5-11, 39-48, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al (WO 99/64850) in view of either McCormick et al or Amigo. Since WO 99/64850 is in German, citations below are given to US Patent No. 6,846,398, which issued from the National Stage entry of this International Application.

Relevant to claims 1 and 46-48, Heller et al disclose a separation device (Figures 1 and 2) comprising: anode and cathode reservoirs (P1 and P2); a plurality of channels connected to the anode reservoirs with each of the channels having an interior bounded by a side wall; a plurality of interface ports (A) formed in the sidewalls of the channels to provide access to the channel, each of the ports having a depth equal to the sidewall (i.e. cover) thickness (Column 6, lines 1-2); with the anode and cathode reservoirs multiplexed with the channels. (Figure 1)

Relevant to claim 39, Heller et al disclose a method of injecting a liquid into their separation device, comprising: connecting a cathode reservoir to the respective first ends of two or more channels; connecting an anode reservoir to the respective second ends of these channels (Figure 1; Column 4, lines 27-31; construction of the device inherently includes steps as recited); forming a droplet of the sample and directing it through an interface port (Column 6, lines 20-28 and 50-52); and applying a voltage to the port in order to inject the sample into the channel. (Column 3, lines 30-32; the charged pin will inherently carry a voltage to the port in the injection step)

Relevant to claims 40 and 43, Heller et al disclose a method of forming a separation device comprising the steps of: forming a plurality of separation channels in the device, each channel being defined by an interior bounded by a side wall; forming a plurality of fluid interface ports (Figure 2, port A) leading to the channels; connecting an anode reservoir to two or more channels; and connecting a cathode reservoir to two or more channels. (Column 4, lines 27-31; construction of the device inherently includes steps as recited)

Relevant to claim 2, Heller et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Figure 1; Electrodes E1-E4)

Relevant to claim 3, the device of Heller et al has an outer perimeter (Figure 1), and the central channels S connect a portion of this perimeter to the center of the device.

Relevant to claim 6, Heller et al disclose such an array of apertures (Figures 1 and 2)

Relevant to claims 7, 41, and 44, Heller et al disclose channel widths of 20 - several hundred microns, and the port diameter is bounded by the channel width. (Figure 2; Column 4, lines 61-62; Column 5, lines 21-25)

Relevant to claim 8, Heller et al disclose their device being a capillary array electrophoresis plate. (Figure 1; Column 1, lines 5-10)

Regarding the independent claims, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as "coplanar" with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Heller et al do not explicitly disclose the thickness of their cover, which is pertinent to the dimensional limitations of the instant claims, an interface port wider than it is deep, or a "virtual wall" meniscus.

McCormick et al disclose a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 13, lines 17-22)

Amigo discloses a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 8, lines 1-6)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device and methods of Heller et al by specifically using a cover as thin as 10 microns, as taught by either McCormick et al or Amigo, because the silence of Heller et al concerning this indicates that a skilled artisan could choose any suitable cover thickness such as those known in the prior art, e.g. McCormick et al or Amigo. The choice of thinner material could be motivated by reduction of material consumption, which could potentially reduce manufacturing costs.

Designation of a channel as a “separation” channel in structural limitations is not given undue weight in these rejections, as it points to an intended use of a device rather than defining a specific structure. The presence of the ports of Heller et al in channel sidewalls meet the structural limitations of the claims.

Regarding the independent claims, within this combination, with a channel and port width of twenty to hundreds of microns (Heller et al; Column 4, lines 61-62; Figure

2) and cover thickness of 10 microns, the limitation to a port diameter significantly larger than its depth is met.

Regarding the limitations to a "virtual wall" and port dead volume of less than a picoliter or zero, Heller et al provide no explicit disclosure except that all channels in their system are filled with a separation medium (Column 5, lines 66-67), and therefore a medium/air interface will exist at these ports. Whether the medium forms a meniscus at the interior or exterior surface of the port depends on the cross-sectional area of the port vs. that of the channel - fluid will naturally be drawn into the narrower opening, driven by its surface tension. While no explicit channel depth is recited by Heller, a shallow channel could obviously be used (e.g. about twice as wide as it is deep, as conventionally results from isotropic glass etching). An approximately hemicylindrical 100 micron wide, 50 micron deep channel would have a cross section of 1250π square microns, while the port configuration of Figure 2 of Heller et al for this channel would be a circle with 100 micron diameter, having a cross section twice as large. In the absence of applied pressure, fluid in the channel would not be drawn into the port to a significant extent, and the meniscus would form at the bottom surface of the wall, leading to a port dead volume of substantially zero. Given a conventional flowable separation medium, this meniscus could only correspond to the instantly claimed "virtual wall", as no distinction between the respective ports, associated channels, or fluids can be seen. In addition, relatively deep channels with larger cross section than that of the port taught by Heller et al could also obviously be used, and in such cases fluid would be drawn into the port, forming a meniscus according to the limitations of claim 50.

Specific to claims 9-11, such limitations to intended use of a system do not further structurally define the claimed device, and the claims are therefore rendered obvious for the same reasons cited above regarding claim 1.

Regarding claims 42 and 45, choice of a radial or other conventional channel pattern is a matter of design choice to a skilled artisan based on which design is most suitable for the peripheral devices to be used with the system. In the absence of evidence that the shape is significant to system operation, such selection of shape does not confer patentability. For instance, in *In re Dailey*, 357 F.2d 669, 149 USPQ 47 (CCPA 1966), the court held that the configuration of the claimed object was a matter of choice which a person of ordinary skill in the art would have found obvious absent persuasive evidence that the particular configuration of the claimed container was significant.

13. Claims 12-24 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al in view of Bjornson et al (US 6,284,113) and either McCormick et al or Amigo.

Relevant to claim 12, Heller et al disclose a separation device (Figures 1 and 2) comprising: an array of microfabricated channels (I and S) formed in a substrate and covered by a cover (Column 5, lines 10-12; Column 6, lines 1-2) anode and cathode reservoirs (P1, P2, reservoirs for E3, E4); the channels having an interior bounded by a side wall (i.e. the cover); a plurality of interface ports (A) formed in the sidewalls of the channels to provide access to the channel, each of the ports having a depth equal to the

sidewall (i.e. cover) thickness (Column 6, lines 1-2); with the anode and cathode reservoirs connected at the ends of the channels. (Figure 1)

Relevant to claim 13, Heller et al disclose channel widths of 20 - several hundred microns, and the port diameter is bounded by the channel width. (Figure 2; Column 4, lines 61-62; Column 5, lines 21-25)

Relevant to claims 16 and 22, Heller et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Figure 1; Electrodes E1-E4)

Relevant to claim 18, Heller et al disclose such a regularly-spaced array of apertures (Figures 1 and 2; regular spacing of ports would be provided for the regularly spaced channels)

Relevant to claim 20, the combined number of ports and application areas/holes in Heller et al is as claimed.

Relevant to claim 23, Heller et al show a plurality of ports in channel I. (Figures 1 and 2)

Relevant to claim 26, Heller et al disclose their device being a capillary array electrophoresis plate. (Figure 1; Column 1, lines 5-10)

Regarding claim 12, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as "coplanar" with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Heller et al do not explicitly disclose the thickness of their cover, which is pertinent to the dimensional limitations of the instant claims, an interface port wider than it is deep, a "virtual wall" meniscus, or arrays of anode and cathode reservoirs as claimed.

McCormick et al disclose a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 13, lines 17-22)

Amigo discloses a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 8, lines 1-6)

Bjornson et al teach the benefits of highly parallel analyses made possible by providing a large number of microfluidic electrophoresis systems in a single chip. (Figures 6-8; Column 25, line 37 - Column 26, line 54)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device and methods of Heller et al by specifically using a cover as thin as 10 microns, as taught by either McCormick et al or Amigo, because the silence of Heller et al concerning this indicates that a skilled artisan could choose any suitable cover thickness such as those known in the prior art, e.g. McCormick et al or Amigo. The choice of thinner material could be motivated by reduction of material consumption, which could potentially reduce manufacturing costs.

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Heller et al by providing a chip having an array of the microfluidic devices of Heller et al, as taught by Bjornson et al, because Bjornson et al teach the desirability of parallel analyses being performed in an array of microfluidic devices on a single substrate. The desirability of such parallel capability would have been obvious to a skilled artisan.

Designation of a channel as a “separation” channel in structural limitations is not given undue weight in these rejections, as it points to an intended use of a device rather than defining a specific structure. The presence of the ports of Heller et al in channel sidewalls meet the structural limitations of the claims.

Regarding claim 12, within this combination, with a channel and port width of twenty to hundreds of microns (Heller et al; Column 4, lines 61-62; Figure 2) and cover thickness of 10 microns, the limitation to a port diameter significantly larger than its depth is met.

Regarding the limitations to a “virtual wall” and port dead volume of less than a picoliter or zero, Heller et al provide no explicit disclosure except that all channels in their system are filled with a separation medium (Column 5, lines 66-67), and therefore a medium/air interface will exist at these ports. Whether the medium forms a meniscus at the interior or exterior surface of the port depends on the cross-sectional area of the port vs. that of the channel - fluid will naturally be drawn into the narrower opening, driven by its surface tension. While no explicit channel depth is recited by Heller, a shallow channel could obviously be used (e.g. about twice as wide as it is deep, as

conventionally results from isotropic glass etching). An approximately hemicylindrical 100 micron wide, 50 micron deep channel would have a cross section of 1250π square microns, while the port configuration of Figure 2 of Heller et al for this channel would be a circle with 100 micron diameter, having a cross section twice as large. In the absence of applied pressure, fluid in the channel would not be drawn into the port to a significant extent, and the meniscus would form at the bottom surface of the wall, leading to a port dead volume of substantially zero. Given a conventional flowable separation medium, this meniscus could only correspond to the instantly claimed "virtual wall", as no distinction between the respective ports, associated channels, or fluids can be seen.

Specific to claims 27-29, such limitations to intended use of a system do not further structurally define the claimed device, and the claims are therefore rendered obvious for the same reasons cited above regarding claim 12.

Specific to dependent claims 14, 15, and 21:

In addition to the obviousness arguments made above, Heller et al do not teach the particular materials claimed. Heller et al are silent concerning the materials from which their devices are formed.

Bjornson et al teach making microfluidic devices from glass, plastic, or a combination thereof. (Column 21, lines 35-43)

It would have been obvious to one having ordinary skill in the art to modify the system of Heller et al by forming the device from glass, plastic, or a mixture thereof, as

taught by Bjornson et al, because Bjornson et al teach that such materials are suitable for making microfluidic devices for electrophoresis. The silence of Heller et al on this subject would have caused a skilled artisan to turn to the related prior art, such as Bjornson et al, for teaching of proper materials.

Specific to dependent claims 17, 19, and 24:

In addition to the obviousness arguments made above, Heller et al do not teach electrodes integral to the substrates.

Bjornson et al teach depositing electrodes directly on a microfluidic device, in contact with the reservoirs thereof. (Column 20, lines 39-45)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the system of Heller et al by providing electrodes deposited directly on the substrate in contact with the reservoirs, as taught by Bjornson et al, because this would eliminate the need for manufacture of a separate electrode plate, and simplify electrical connection to the fluids within the device by eliminating concerns regarding precise alignment. Such deposited arrays meet the limitations of these claims.

14. Claims 1-3, 5-8, 12-24, 26, 30-36, and 38-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al in view of Howitz et al.

Relevant to claim 1, Simpson et al disclose a separation device (Column 1, line 65 - Column 2, line 1) comprising: one or more anode reservoirs (Figure 1, 180;

Column 9, lines 25-27)); a plurality of separation channels connected to the anode reservoirs (Column 3, lines 14-28; Column 9, lines 25-27), with each of the separation channels having an interior bounded by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); a plurality of fluid inlets to the separation channels (Figure 2, B and C with associated channels to channel 222); and at least one cathode reservoir multiplexed with two or more separation channels. (Figure 1, Reservoir 120)

Relevant to claim 12, Simpson et al disclose a separation device comprising: an array of microfabricated separation channels formed at the surface of a first microfabricated substrate and a corresponding surface of a second substrate bonded to the surface of the first substrate with each channel having an interior bounded by a sidewall, a first end and a second end (Figures 1 and 4B; Column 9, lines 12-17; Column 4, line 47 - Column 5, line 7); an array of fluid inlets to the separation channels (Figures 1 and 2, B and C with associated channels to channel 222); an array of cathode reservoirs connected to the first end of each of the separation channels (Figure 1; Column 9, lines 23-24); and an array of anode reservoirs, wherein at least one anode reservoir is connected to the respective second ends of at least two of the separation channels. (Figure 1; Column 9, lines 25-27)

Relevant to claims 30 and 32, Simpson et al disclose a separation device comprising: a substrate (Column 4, line 47 - Column 5, line 7); a plurality of separation channels formed in the substrate (Column 3, lines 14-28), each channel having an interior bound by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); a plurality of fluid inlets to the separation channels (Figure 2, B and C with associated channels to

channel 222); an anode reservoir multiplexed to two or more separation channels (Figure 1, Reservoir 180; Column 10, lines 49-57); and a cathode reservoir multiplexed to two or more separation channels (Figure 1, Reservoir 120; Column 10, lines 58-65)

Relevant to claims 2, 16, 17, 22, and 34, Simpson et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Column 5, line 36 - Column 6, line 37; Column 10, lines 9-10) This array can be in electrical contact with the device (Figure 4B; Column 10, lines 31-33), or integral with the substrates of the device (Column 10, lines 11-13).

Relevant to claim 3, Simpson et al disclose a separation device with an outer perimeter and a center, with the separation channels connecting the outer perimeter to the center. (Figure 9; Column 9, lines 9-11)

Relevant to claims 8 and 26, Simpson et al disclose their device being a capillary array electrophoresis plate. (Column 1, lines 65-66)

Relevant to claim 14, Simpson et al disclose the first and second substrates being made of glass. (Column 9, lines 66-67)

Relevant to claim 15, Simpson et al disclose the first and second substrates being made of plastic. (Column 10, lines 1-2)

Relevant to claims 18 and 35, Simpson et al disclose the regular spacing of the fluid inlets on one of the substrates to receive solutions from a parallel loading device. (Column 1, lines 13-15; Column 4, line 47 - Column 5, line 7)

Relevant to claims 19 and 24, Simpson et al disclose the first substrate of their device including an array of electrodes aligned with sample reservoirs of the device to

make electrical contact with solutions in the sample, waste, anode, and cathode reservoirs. (Column 10, lines 17-23)

Relevant to claim 20, Simpson et al disclose a number of holes, H, approximately equal to 5N/4, where N is the number of samples to be processed. (Column 10, lines 24-27)

Relevant to claim 21, Simpson et al disclose their device being made of a combination of glass and plastic. (Column 10, lines 28-30)

Relevant to claim 23, Simpson et al disclose a plurality of sample fluid inlets in communication with on of the separation channels (e.g. Figure 2, B and C both feed channel 222)

Relevant to claim 36, Simpson et al disclose a parallel loading device comprising a multi-headed pipetter. (Column 11, lines 16-18)

Relevant to claim 38, Simpson et al disclose the disposition of the separation channels in a radial pattern on the separation device. (Figure 9)

Relevant to claim 39, Simpson et al disclose a method of injecting a liquid into their separation device, comprising: connecting a cathode reservoir to the respective first ends of two or more channels (Column 11, lines 29-30); connecting an anode reservoir to the respective second ends of these channels (Column 11, lines 31-32); loading a sample liquid into the sample reservoir; and applying a voltage to inject the sample into the separation channel. (Column 8, lines 32-41; Column 11, lines 33-41)

Relevant to claims 40 and 43, Simpson et al disclose a method of forming a separation device comprising the steps of: forming a plurality of separation channels in

the device (Column 11, line 49), each channel being defined by an interior bounded by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); forming a plurality of sample reservoirs connected to the channels (Column 11, lines 50-54); connecting an anode reservoir to two or more channels (Column 11, lines 55-56); and connecting a cathode reservoir to two or more channels. (Column 11, lines 66-67)

Relevant to claims 42 and 45, Simpson et al disclose the radial disposition of the channels on the separation device. (Figure 9)

Regarding the independent claims, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as "coplanar" with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Simpson et al do not explicitly disclose a device comprising: fluid interface ports formed in the side walls of the separation channels to provide access to the interiors of the separation channels, wherein the diameter of the port is significantly larger than its depth, wherein a separation medium disposed in the interior of the separation channel forms a virtual wall at each fluid interface port, and wherein each fluid interface port has a dead volume less than about 1 pL (Claim 1), zero dead volume (Claim 5), or diameters between 25 and 125 μm. (Claims 7, 13, 25, 31, 33) They also do not explicitly disclose a fluid interface port that comprises an array of apertures forming virtual walls. (Claim 6)

Regarding claim 39, Simpson et al do not explicitly disclose forming a droplet from the liquid sample, or directing the droplet to a virtual wall formed by a separation medium in a fluid interface port formed in the sidewall of a separation channel.

Regarding claims 40-45, they also do not explicitly disclose a method comprising forming the plurality of ports in the channel sidewalls by removing portions of the sidewalls to define ports with diameters between 25 and 125 μm.

Howitz et al disclose a device (Figure) comprising: fluid interface ports (capillaries containing menisci 6) formed in the side wall of a fluid channel (9) to provide access to the interior of the fluid channel, wherein a separation medium disposed in the interior of the fluid channel forms a virtual wall at each fluid interface port (Menisci 6). (Column 3, lines 11-15) Relevant to claim 6, they also disclose a fluid interface port comprising an array of apertures forming virtual walls.

Relevant to claim 39, Howitz et al disclose a method of sample injection comprising: forming a droplet from the liquid sample (Figure, droplet 5; Column 3, lines 31-34), and directing the droplet to a virtual wall formed by a liquid in a fluid interface port formed in the side wall of a flow channel.

Relevant to claims 40-45, they also disclose a method of forming their fluid interface ports, comprising the step of forming fluid interface ports in the channel sidewalls with diameter between 25 and 125 μm. (Column 3, lines 12-15, length and width are 50 μm)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Simpson et al by replacing the sample and waste reservoirs, and their associated side channels with a simple hole or holes through the sidewall to serve as a fluid port, as taught by Howitz et al, because Howitz et al teach the usefulness of their fluid port in introducing fluids to microchannels while preventing outflow of the fluid contained within the channel. (Column 1, lines 53-58) It would also reduce the number of holes required in the device by eliminating the need for injection crosses, this reduction in the number of holes having been taught by Simpson et al to be desirable. (Column 3, lines 50-65)

Further addressing claims 1 and 5, given the definition of dead volume presented in the instant specification (roughly, the volume of liquid held in the port and not flowing with the fluid within the channel), the dead volume associated with ports such as those of Howitz et al will be variable, as a function of the affinities of the fluids for the surface of the port, among other factors. (Column 3, lines 25-31) As such, the dead volume will be zero or near zero (i.e. less than 1 picoliter) for a clean hydrophobic port surface in a device using aqueous fluids. Such hydrophobicity is an innate property of many polymers known to be useful in manufacturing microfluidic devices (e.g. fluoropolymers) or it could be achieved by using known surface treatments for glass (hexamethyldisilazane, used by Simpson - Column 4, lines 53-56) and silicon (Hydrofluoric acid), and would constitute an obvious modification of the device, because such a surface would minimize loss of the injected sample. (i.e. if an aqueous sample hit a hydrophobic surface in a port configured in the way shown in the Figure of Howitz

et al, substantially the entire droplet would immediately fall into contact with the fluid in channel 9, as the contact angle and reduced frictional force would not be sufficient to retain the droplet on this surface)

Regarding the limitation that the port be wider than it is deep, although the example given by Howitz et al does not meet this limitation, Howitz et al also disclose variation of the depth of the port. (i.e. length of the capillary; Column 2, lines 5-10 and 27-30) Choice of a shorter length such that this limitation is met would have been obvious to a skilled artisan, particularly given the trend towards miniaturization in this art.

Further addressing claim 20, by replacing each sample reservoir with a fluid interface port, and eliminating waste reservoirs, the number of holes in this combination device would be reduced to N+A+C, where N is the number of samples to be analyzed, A is the number of anode reservoirs, and C is the number of cathode reservoirs.

Regarding claim 39, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Simpson et al by altering the injection step by: forming a droplet of the sample and directing it to the virtual wall formed at a fluid interface port by a liquid in the separation channel (in the combination device of Simpson et al and Howitz et al described above), as taught by Howitz et al, because it would reduce waste of the sample liquid.

Regarding claims 40-45, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Simpson et al by replacing the step of forming sample reservoirs and associated side channels with the

formation of a simple hole or holes (50 μm length and width) through the sidewall to serve as a fluid port, as taught by Howitz et al, because Howitz et al teach the usefulness of their fluid port in introducing fluids to microchannels while preventing outflow of the fluid contained within the channel. It would also reduce the number of holes required in the device by eliminating the need for injection crosses, this reduction in the number of holes having been taught by Simpson et al to be desirable. (Column 3, lines 50-65)

Regarding claims 46-48, each of these claims fully encompasses claim 1 in that they only recite limitations that are present in claim 1, while removing various other limitations. The prior art as applied to claim 1 above therefore also renders these claims obvious, given their open language (i.e. "comprising").

15. Claims 9-11 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al and Howitz et al as applied to claims 1 and 12 above, and further in view of Bjornson et al. (US 6,103,199)

Simpson et al and Howitz et al disclose combinations as described above in addressing claims 1 and 12.

Neither Simpson et al nor Howitz et al disclose their devices being used for electrochromatography (Claims 9 and 27), pressure-driven chromatography (Claims 10 and 28), or isoelectric focusing (Claims 11 and 29).

Bjornson et al disclose electrophoretic devices used for isoelectric focusing and capillary chromatography. (Column 12, lines 53-59) They also disclose fluid flow in

their devices by electroosmosis (Column 11, lines 55-60), which suggests electrochromatography. (i.e. chromatography in which the motion of the mobile phase is caused by an electric field)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of Simpson et al and Howitz et al by providing the separation capillaries with a chromatographic medium, immobilized pH gradient, or ampholytes and using the device for electrochromatography or isoelectric focusing, as taught by Bjornson et al, because it would provide useful analytical data about the analytes. It would be well within the abilities of one having ordinary skill in the art to use the channel structure shown by Simpson et al with any known prior art capillary electrophoretic technique, such as those claimed here.

Additionally, electroosmotic force corresponds to a type of pressure driving a fluid through a capillary, and as such, is considered a form of pressure-driven chromatography.

16. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al and Howitz et al as applied to claim 36 above, and further in view of Sundberg et al.

Simpson et al and Howitz et al disclose a combination as described above in addressing claim 36. Simpson et al and Arnold et al also disclose a combination as described above in addressing claim 36.

None among Simpson et al, Howitz et al, and Arnold et al disclose a parallel loading device comprising a pin for carrying and introducing the droplet of a liquid sample to the fluid interface port by contacting the virtual wall.

Sundberg et al disclose a parallel loading device (Figure 2) comprising a pin (38) for carrying and introducing the droplet of a liquid sample (36) to the ports (34) of a microfluidic system.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of either Simpson et al and Howitz et al or Simpson et al and Arnold et al by providing a parallel loading device comprising pins for carrying liquid samples to the fluid interface port, as taught by Sundberg et al, because it would simplify delivery of small droplets. It would be well within the abilities of one having ordinary skill in the art to choose any known means of delivering fluid droplets to a selected spot in a microfluidic device (i.e. the port), such as that taught by Sundberg et al. A technique that delivers a plurality of droplets simultaneously, such as that of Sundberg et al, would be particularly obvious to choose, because it would aid in increasing throughput, decreasing labor, etc.

Response to Arguments

17. Applicant's arguments filed 11 December 2006 have been fully considered but they are not persuasive.

Regarding the rejection of claim 50 under 35 U.S.C. §112, first paragraph, Applicant cites page 10, line 8 as providing support for the limitation requiring that "an

inner edge of the meniscus aligns with an inner surface of the side wall and an outer edge of the meniscus aligns with an outer edge of the side wall". Page 10, line 8 of the specification states that "[t]he meniscus essentially replaces the removed portion of the side wall that defines the aperture 17". This cited section is part of a description of Figure 4A (Page 10, lines 1-20), and Figure 4A clearly shows a meniscus in which an inner edge of the meniscus is not aligned with any portion of the outer wall, and an outer edge of the meniscus is aligned with an inner edge of the side wall. The described replacement of the portion of the side wall is open to any number of equally valid interpretations. The Examiner would maintain that any meniscus circumferentially anchored anywhere along the sides of aperture 17 corresponds equally well to this replacement of the portion of the side wall, and Applicant is attempting to impose one arbitrary reading long after the filing of the application. There is simply no support in the originally filed application for the limitations of claim 50.

Applicant further contends that if the replacement were not as described in claim 50, the wall portion would not be replaced by the meniscus, but rather by a combination of air and/or fluid. The Examiner must point out that even if the meniscus were as claimed in claim 50, a combination of air and liquid is present inside aperture 17. This is completely inevitable, since a meniscus is a surface and therefore is not capable of completely occupying a three-dimensional space.

Applicant further cites the possibility of zero dead volume as somehow requiring the meniscus to be as claimed in claim 50. In fact, if the meniscus were as recited in claim 50, it would be physically impossible for the port/virtual wall/meniscus to have

zero dead volume. The portion of liquid along the upper portions of the sides of aperture 17 would not flow with the fluid passing through the channel, but be retained within the port. The volume occupied by this liquid would be considered dead volume, according to Applicant's specification. (Page 11, lines 17-25)

Regarding the definition of coplanar, Applicant argues that the plane of the meniscus is equal to, not a subset of the coplanar plane of the side wall. This is problematic for at least the following reasons: (a) a meniscus is not planar, (b) numerous planes are defined by the side wall, including the plane of its upper and lower surfaces, (c) no such narrow definition of "coplanar" is supported by the original disclosure. The meniscus cannot rigidly be bound to be <u>entirely</u> within a single plane, since by its nature it is a curved surface. The definition from Webster's Third International Dictionary, that "coplanar" is defined as "lying or acting in the same plane". Based on these considerations, the most reasonable position seems to the Examiner to be that any meniscus having a portion lying in any plane defined by the side wall as "coplanar" with the side wall. Unlike Applicant's proposed reading, this would be consistent with Applicant's disclosure. (e.g. Figures 4A-4G show menisci that do not correspond to Applicant's reading; page 10, lines 17-20 describe menisci that do not correspond to Applicant's reading) In fact, there is no disclosure of a meniscus corresponding to the reading presented in Applicant's remarks in the specification as originally filed. Therefore the reading relied upon by the Examiner is considered to be the appropriate one.

Applicant argues that the ports of Heller et al are not formed in a side wall. As clearly disclosed by Heller et al and referenced in the rejections above, application areas A can be open areas in a film that covers the separation channels. (i.e. holes in the cover). The cover of Heller et al can be considered as providing a side wall, just as in each and every embodiment described in the instant application. The Examiner cannot imagine what distinction Applicant is trying to point out in this argument.

Applicant also argues that the ports of Heller et al are not in separation channels. The term "separation" adds no structure to the claim, and the Examiner's position throughout prosecution has been that any channels having ports as claimed read on these limitations. Whether Heller et al use the channels having the ports for separation is immaterial - the structure they disclose corresponds to that claimed.

Applicant also reiterates arguments that Heller et al do not teach the "virtual wall", "coplanar", and "dead volume" limitations. For the reasons cited in the rejections and remarks above, such features are inherently taught or obvious over the teachings of the prior art. Any recited limitations that merely describe the way in which a fluid behaves in a channel having a hole in its side must be considered inherent over the structures taught, for example, by Heller et al or Singh et al, because the channel/port structures taught by these references are the same as those instantly claimed. Once liquid is added to the channels, the liquid must be considered to behave precisely the same as long as there is no structural difference between the claims and the prior art. Applicant must claim structure that distinguishes the claimed subject matter from the prior art in order for the claims to be allowable.

Applicant argues that if Howitz were modified as suggested by the Examiner, it would be inoperable for its intended purpose, because the efficiency of loading would be compromised by the smaller fluid interface port. There is nothing in the Howitz reference that indicates that any reduction in efficiency would result from miniaturization, and nowhere in the rejections is the size of the port openings in Howitz altered - the Examiner relies on Howitz's teaching that capillary length can be altered, but this requires no modification of port opening size.

Applicant also argues that substantial reconstruction and redesign would be required in the combinations made, as well as a change in the basic principle of operation. It is not clear which rejection Applicant is referring to, but no particular redesign of Heller et al is made in the rejections above - the most substantial secondary teaching is cover thickness. In Simpson et al, one injection means is replaced by that of Howitz, which is advantageous for the reasons given in Howitz. This hardly constitutes substantial redesign, and there is no change in basic principles of operation contemplated in the rejections above.

Applicant further argues that the prior art teaches towards maximizing dead volume. In fact no artisan seeking to transfer a fluid into a channel would attempt to maximize dead volume - modifications made above towards minimizing dead volume correspond to the <u>universal</u> desire of those in the art to maximize efficiency in fluid transfer (i.e. reduction of dead volume), which is by no means the exclusive domain of Applicant.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Jeffrey T. Barton whose telephone number is (571) 272-1307. The examiner can normally be reached on M-F 9:00AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam Nguyen can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JTB
14 March 2007

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